REMARKS

By this amendment claim 12 is canceled; claims 9 and 22 are amended; and claims 26 and 27 are added.. Claims 9, 10, 17, 18, 20 and 22-27 are pending. Claim 12 is rewritten as claim 26. Claim 12 had a typographic error in the previous amendment and is rewritten as claim 26 for clarity. New claim 27 finds support in the application, for example, at page 5, penultimate paragraph. The dependence of claims 9 and 22 is changed to recite new claim 26. No issue of new matter arises.

Rejection under 35 U.S.C. §103(a)

Claims 9, 10, 12, 17, 18, 20, 22-25 were rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Citron in view of St. George-Hyslop, Ishii, Borchelt, Xia and Lombardi. Applicants respectfully traverse this rejection.

The application has two independent claims, claims 20 and 26. Each independent claim recites: "a multimutated form of presenilin 1, wherein the mutations are M146L, H163R, A246E, L286V and C410Y, and allowing an apoptotic phenomenon to be detected in a renewable peripheral tissue." All pending claims include these limitations as provided by 35 U.S.C. §112, fourth paragraph.

In explaining the rejection, the Office Action applies Citron as teaching:

> that Abeta42 is elevated in conditioned media of cells expressing mutant but not wild type presenilin 1 (PS1). Further, the effects of two different PS1 mutations are additive when engineered into the same PS1 molecule (Citron et al., abstract). Citron et al. teach that kidney cells were stably transfected with APP695 and a PS1 double mutant and that these cells had higher levels of Abeta42 than cells that have single mutations in PS1 (Citron et al. page 111, 2nd col., under Abeta42 Effects of the PS1 Mutations M146L and L286V Are Additive).

At page 3, penultimate paragraph, the Office Action concludes:

> Citron et al. teach that presenilin mutations have a systemwide effect of Abeta42 production and can therefore be studied in a **peripheral cell line** (Citron et al., page 112, 1st col. under Discussion). Citron et al. also teach that cells that

> predominantly make the Abeta42 protein will be useful for localizing the subcellular sites of Abeta42 production and understanding the way in which mutant presenilin alters APP proteolysis. By additional manipulations, it would be possible to generate cell lines and transgenic animals which would produce almost exclusively Abeta42 (Citron et al. page 115, 1st col., 1st parag.).

(Applicants make one point for clarification. The expression bolded above refers to a peripheral cell line. A cell line refers to cells capable of being cultured. Cell lines are not the same as simple peripheral cells, which are primary cells, extracted directly from the organism, not cells maintained in culture. Thus the peripheral cell line of Citron does not suggest the primary cells featured in the claims of the present application.)

The Office Action then acknowledges and concludes:

> While Citron et al. do not specifically teach that transgenic mice comprising multiple mutations in PS1 exhibit apoptosis in their peripheral cells, this would be an inherent characteristic of these transgenic mice.

Applicants respectfully submit that inherency of a transgenic animal is not a proper issue in rejecting these claims. The claims claim methods, not transgenic animals. Citron, as acknowledged in the Office Action, does not teach this feature.

Then, in an attempt to remedy this acknowledged deficiency, at page 4, first paragraph, last sentence, the Office Action alleges:

> It is noted, that the art at the time of filing teaches that peripheral cells that express mutant PS1 exhibit apoptosis (St. George-Hyslop et al., col. 20, 3rd parag.).

Applicants respectfully submit that St. George-Hyslop (6395960) was incorrectly cited. Whether the Office Action referenced the third paragraph or third complete paragraph, no mention of apoptosis is found:

> The normal PS1 protein, substantially free of other proteins, is encoded by the aforementioned SEQ. ID No:1 and SEQ ID NO:133. As will be later discussed, PS1 protein and fragments thereof may be made by a variety of methods. Purified mutant PS1 protein is characterized by FAD--associated phenotype

(necrotic death, apoptotic death, granulovascular degeneration, neurofibrillary degeneration, abnormalities or changes in the metabolism of APP, Ca.sup.2+, K.sup.+, and glucose, mitochondrial function and energy metabolism neurotransmitter metabolism, all of which have been found to be abnormal in human brain, and/or peripheral tissue cells in subjects with Alzheimer's Disease) in a variety of cells. The mutantPS1, free of other proteins, is encoded by the mutant DNA sequence.

Mutations in the S182 (PS1) Transcript

Several mutations in the ARMP gene have been identified which cause a severe type of familial Alzheimer's Disease. One or a combination of these mutations may be responsible for this form of Alzheimer's Disease as well as several other neurological disorders. The mutations may be any form of nucleotide sequence alteration or substitution. Specific disease causing mutations in the form of nucleotide and/or amino acid substitutions have been located, although it is anticipated that additional mutations will be found in other families.

The only "apoptosis" reference found in St. George-Hyslop explicitly mentions apoptosis in the context of a non-peripheral tissue, i.e., a part of the central nervous system, the brain [Emphasis added.]. See St. George-Hyslop at column 44, lines 53-59:

> The effect of these mutations in PS1 and PS2 apprently [sic] is a gain of a novel function or an acceleration of a normal function which causes aberrant processing of (APP) Amyloid Precursor Protein into Aβ peptide, abnormal phosphorylation homeostasis, and abnormal **apoptosis in brain**.

In the paragraph bridging pages 4 and 5, the Office Action continues this line of the rejection :

> With regard to the claims being drawn to the cells being T-lymphocytes (claims 10, 18), it is noted at the time of filing, the art know of the relationship between T-cells and apoptosis. **First**, as indicated above, St. George-Hyslop et al. teach that peripheral cells that express mutant PS1 exhibit apoptosis. **Second**, Lombardi et al. teach that populations of T -cells were lower in Alzheimer's

patients versus that of normal patients and that T cells underwent apoptosis. [Emphasis added.]

The first reason is not supported by the referenced document as discussed above. The second reason relates a situation in patients, not a transgenic mouse and merely mentions the fact, that like other cells, T-cells can undergo apoptosis. There is no teaching or suggestion that multi-mutated transgenic animals or cells therefrom would be successful tools for use in assays as shown in the examples and figures of the present application.

The Office Action accordingly fails to establish a *prima facie* case of obviousness in at least this aspect of the rejection. Reconsideration and withdrawal of this rejection are respectfully requested.

Additionally, the Office Action at page 4, first complete paragraph, also proposes:

> With regard to the claims being drawn to PS1 comprising at least 3 mutations or 5 particular mutations (e.g. claims 4, 5), these are known mutations in PS1 and given that Citron et al. teach that it would be ideal to make a transgenic mouse that produces almost exclusively Abeta42, an artisan would have made mice comprising additional mutations in PS1, to arrive at mice that produce more Abeta42 than the double mutant PS1 mouse made by Citron et al.

And at page 5, fourth paragraph continues this line with the observation:

> Applicant indicates that claims 12 and 20 are amended and recite 5 specific mutations not taught or suggested by the applied references (Applicant's response, page 4). In response, this is not persuasive. As indicated above, the mutations M146L and L286V are taught by Citron et al., the H163R mutation is taught by Ishii et al., the A246E mutation was taught by Borchelt et al., and the C410Y mutation was taught by Xia et al.

Applicants respectfully submit that the Office Action here merely lists 5 mutations of scores of mutations known in the art. In an unpredictable art such as this there is no reasonable expectation that any randomly selected set of mutations would produce desired results. Here the Office Action apparently relies on the present application to craft the rejection based on

hindsight reasoning. For at least this additional reason Applicants respectfully request reconsideration and withdrawal of this rejection.

At page 5, first complete paragraph, The Office Action comments:

> With regard to the claims being drawn to "allowing an apoptotic phenomenon to be detected in a renewable peripheral tissue" (e.g. claim 12), it is not entirely clear what this phrase means. However, the Examiner has interpreted this to mean that changes in apoptotic activity in peripheral tissues are detected and that an artisan would have identified compounds that treat apoptosis by identifying the compounds that reduce apoptosis.

Applicants wish to clarify this comment. Claim 26 (based on previous claim 12) recites: "allowing an apoptotic phenomenon to be detected in a renewable peripheral tissue". Applicants respectfully comment that this phrase is meant to emphasize advantages of the present invention, for example, to distinguish over the St. George-Hyslop teaching that apoptosis could be detected in brain tissue. Monitoring in a peripheral tissue sample has advantages of providing a more practical source of material, not requiring sacrificing the animal. See application p.7, first paragraph. This feature is not appreciated in the applied art and therefore represents an unexpected benefit of the present invention.

For this additional reason reconsideration and withdrawal of this rejection are respectfully requested.

Conclusion

In view of the above amendments and remarks, Applicants respectfully submit that the application is now in condition for allowance and request prompt issuance of a Notice of Allowance. Should the Examiner wish to suggest additional changes that might put the application in even better condition for allowance, the Examiner is requested to contact the undersigned at the telephone number listed below.

Fees

The Commissioner is hereby authorized to charge any fee required for added claims and any additional fees that may be needed to Deposit Account No. 18-1982.

Respectfully submitted,

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